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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,237	03/06/2002	Steven T. Boyce	CUT/01	8680

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,237	BOYCE, STEVEN T.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 10, 18, 24, 28-29 and 32 are amended.

Claims 34-37 are newly filed.

Claims 1-37 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***703-872-9306****.*

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/26/04 has been entered.

Claim Rejections - 35 USC § 102

*The rejection of claims 1-10, 13-29 and 31-33 under 35 U.S.C. 102(b) as being anticipated by Boyce (Med. Biol. Eng. Comput. 36:791-800, 1998, ref of record) has been withdrawn in view of interview conducted on 07/29/04, applicant's declaration and response filed on 08/26/04. The cited art clearly teaches skin substitutes comprising cultured dermal cells on Collagen-GAG matrix, which further provides a lamination layer for cultured keratinocytes. However, the applicant argues that figure-1 of the prior art (**applicant's own publication**) does not anticipate the invention as claimed, since the prior art does not enable the claimed invention as there is no reasonable expectation of success of achieving the claimed invention without extensive and complex experimentation i.e. undue experimentation (see response filed 8/26/04, page 10-11).*

Claim Rejections - 35 USC § 103

*The rejection of claims 11-12 and 30 under 35 U.S.C. 103(a) as being unpatentable over Boyce (Med. Biol. Eng. Comput. 36:791-800, 1998, ref of record) as applied to claims 1-10, 13-29 and 31-33 above, and further in view of Boyce (US 5,976,878, 1999, ref of record) has been withdrawn in view of interview conducted on 07/29/04, applicant's declaration and response filed on 08/26/04. The cited art clearly teaches skin substitutes comprising cultured dermal cells on Collagen-GAG matrix, which further provides a lamination layer for cultured keratinocytes. However, the applicant argues that figure-1 of the prior art (**applicant's own publication**) does not anticipate the invention as claimed, since the prior art does not enable the claimed invention as there is no reasonable expectation of success of achieving the claimed invention without extensive and complex experimentation i.e. undue experimentation (see response filed 8/26/04, page 10-11).*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 18, 24, 28-29, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to a cultured skin device comprising cultured dermal cells on an outer surface of a biocompatible reticulated matrix. The specification does not define what is the "outer surface of biocompatible reticulated matrix".

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

So claims 1, 10, 18, 24, 28-29, 32and 34 are apparently new matter. No pages or place in the specification was cited to support this amendment. A careful review by the examiner of the specification failed to identify any support for this new limitation. Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention:

The instant invention relates to an artificial skin construct.

Breadth of Claims and Guidance Provided in the Specification

The scope of invention as claimed encompasses an artificial skin device that mimics natural skin. The artificial skin device as claimed further comprises variety of epidermal (*i.e. keratinocytes, melanocytes, immunocytes, stem cells, and combination thereof*) and dermal cells (*i.e. fibroblasts, endothelial cells, immunocytes, nerve cells, myocytes, stem cells, and combination thereof*). The skin construct as claimed is of therapeutic use in patients with a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, any metabolic disease, any protein defect, any protein deficiency, and combinations thereof. Furthermore the skin device as claimed is capable of providing an epidermal barrier, basement membrane, angiogenesis and pigmentation in patients.

The specification as filed fails to disclose any skin device (claimed) that is capable of engraftment in an animal and can be of any therapeutic use in a patient with a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, any metabolic disease, any protein defect, any protein deficiency, and/or combinations thereof. The examples provided in the specification as filed are prophetic and read as instructions rather than examples, leaving significant amount of experimentation necessary to practice the invention especially in view of applicants remarks filed on 08/26/04.

State of Art and Predictability

The state of the artificial skin art at the time of filing of instant invention was such that the construction artificial skin is complex and the final product made is of little benefit if it cannot be efficiently produced, and is capable of providing engraftment benefits. For example formation of epidermal layers and visualization is critical to engraftment of any skin substitutes. The art the time of filing clearly teaches that incorporation of cells other than fibroblasts and keratinocytes requires optimization of various aspects for the development artificial skin which are not considered routine in the art. For example if the endothelial cells are incorporated in bilayred skin constructs, the endothelial cells are not only selectively lost due to differential growth characteristics but their presence also affects the organization of the epidermal layers due various factors produced by the endothelial cells (see Supp et al. *The FASEB Journal.* 16:797-804, 2002, see page 803, col.1). In instant case the examples provided in the instant application are prophetic and read as instructions rather than examples, leaving significant amount of experimentation necessary to practice the invention. The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). Therefore considering applicant's own assertion (i.e. making a skin construct as claimed is unpredictable) and the limited amount of guidance provided in the instant specification regarding the fate and functional effects of any other cell type in a bilayerd skin construct (i.e any type of stem cells, immunocytes, nerve cells. myocytes and/or combination thereof) in the formation of artificial skin, it is highly unpredictable that such a combination would result in the formation of skin device that is capable of providing any engraftment benefits.

Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case making an artificial skin device wherein the components are not structurally and functionally defined is not considered routine in the art and without sufficient guidance to a specific combination the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-7, 9-11, 13-15, 18-29 and 31-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilkins et al (Biotech. and Bioeng. 43:747-756, 1994).

The invention as claimed is drawn to a skin device comprising cultured epidermal cells and dermal cells cultured on a biocompatible matrix.

Wilkins teaches a human living skin equivalent (LSE) bilayer skin construct for clinical applications (see entire document). With regard to claims 1, 5-6, 10, 13-29 and 31-37, the cited art teaches a cultured skin construct comprising cultured human dermal fibroblast (HDF) on bovine type I collagen matrix, which provides a lamination layer for cultured keratinocytes (HEK). See page 749 col.2, para. 3-4, page 750, col.1 fig-1, 2). With regard to claims 2, 3, 19-20 and 25, the cited art further teaches that components of living skin equivalent include keratinocytes and fibroblasts (page 748, col.2 para.2). With regard to claim 4, and 27 the cited art further teaches the use of skin construct for burns, scars cutaneous ulcers or congenital anomalies (page 747, col.2. page 754, col.1-2). With regard to claims 7 and 21-22 the cited art further teaches that cells in the skin construct are of autologous or allogenic origin (page 748 col.2 para.1). With regard to claim 9 and 26 the cited art further teaches that the skin substitute is capable of providing epidermal barrier after grafting (page 753, fig-8). Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 12, 16-17 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilkins et al (Biotech. and Bioeng. 43:747-756, 1994) as applied to claims 1-7, 9-11, 13-15, 18-29 and 31-37 above, and further in view of Boyce (Med. Biol. Eng. Comput. 36:791-800, 1998, ref of record) and Boyce (US 5,976,878, 1999, ref of record).

Wilkins teaches a human living skin equivalent (LSE) bilayer skin construct for clinical applications (see entire document). With regard to claims 1, 5-6, 10, 13-29 and 31-37, the cited art teaches a cultured skin construct comprising cultured human dermal fibroblast (HDF) on bovine type I collagen matrix, which provides a lamination layer for cultured keratinocytes (HEK). See page 749 col.2, para. 3-4, page 750, col.1 fig-1, 2). With regard to claims 2, 3, 19-20 and 25, the cited art further teaches that components of living skin equivalent include keratinocytes and fibroblasts (page 748, col.2 para.2). With regard to claim 4, and 27 the cited art further teaches the use of skin construct for burns, scars cutaneous ulcers or congenital anomalies (page 747, col.2. page 754, col.1-2). With regard to claims 7 and 21-22 the cited art further teaches that cells in the skin construct are of autologous or allogenic origin (page 748 col.2 para.1). With regard to claim 9 and 26 the cited art further teaches that the skin substitute is capable of providing epidermal barrier after grafting (page 753, fig-8).

Even though Wilkins teaches a method of making skin construct comprising variety of cultured cells the reference does not specifically teach a method of producing a cultured skin device in medium containing insulin in the range of 0.05 ug/ml to 500 ug/ml and incorporation of genetically engineered cells.

Boyce (1998) teaches skin substitutes comprising cultured human keratinocytes, fibroblasts, melanocytes and collagen-GAG polymers. The cited art teaches a cultured skin substitute comprising cultured dermal cells on Collagen-GAG matrix, which further provides a lamination layer for cultured keratinocytes. The cited art further teaches that components of skin substitute include keratinocytes, fibroblasts, endothelial cells, smooth muscle cell, melanocytes, nerve cells, glands and hair follicles (page 792, col. 1, table-1, page 793 fig-1). The cited art further teaches the use of skin substitutes for burns, scars cutaneous ulcers or congenital anomalies (page 791, col.1 para.1). The

cited art further teaches that cells in the skin substitute ranges from culture parenchymal cells (autologous or allogenic) to tissue derivatives (i.e. xenogeneic collagens acellular dermal matrix) to synthetic polymers (page 792 col.2 para.1). With regard to claim 8 the cited art further teaches genetic modification of skin cells (page 797 col.2 para.2-3, page 794 fig-3). The cited art further teaches that the skin substitute is capable of providing epidermal barrier, basement membrane, angiogenesis and pigmentation (page 794 col.1 para.1, col.2 para.1; page 795, col.2 para.1). The cited art further teaches the use of non-adherent highly porous dressing that allow both delivery and drainage of wound exude from grafts during the period of engraftment (page 795, col.2 para.1).

Boyce (1999) teaches a composite skin construct and a method of making the skin constuct. With regard to claims 11-12 Boyce (US 5,976,878, 1999) teaches a method of making a composite skin on a laminated surface of dermal membrane (collagen-GAG), wherein the human keratinocytes are cultured in a media containing 0.5 ug/ml of insulin (col.14 line 64). With regard to claim 30 the cited art teaches dehydration of collagen matrix to form a cross-linked matrix before inoculation with dermal culture (col.12 line 45-61).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to incorporate insulin in the range of 0.05 ug/ml to about 500 ug/ml in the culture conditions as taught by Wilkins in view of Boyce (1999). One would have been motivated to incorporate insulin in culture media because insulin is a growth factor that increases cellular growth and proliferation. It would have been further obvious to use dehydrated laminated collagen as taught by in view of Boyce (1999). One would have been motivated to make dried cross-lined matrix because such a preparation can be stored in a dry state for future use. In addition it would have been further obvious to incorporate genetically engineered cells in the skin construct in view of Boyce (1998). One would have been motivated to do so produced the desired gene product in the cultured skin construct. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

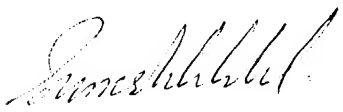
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to ***(571) 272-0547.*** *For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is* ***703-872-9306.***

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.



SUMESH KAUSHAL
PATENT EXAMINER